Title: Comparative effectiveness of enalapril, lisinopril and ramipril in the treatment of patients with chronic heart failure. A propensity score matched cohort study.

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Abstract

Background: Angiotensin converting enzyme inhibitors (ACEIs) are recommended as first-line therapy in patients with heart failure with reduced ejection fraction (HFrEF). The comparative effectiveness of different ACEIs is not known.

Methods and results: 4,723 out-patients with stable HFrEF prescribed either enalapril, lisinopril, or ramipril were identified from three registries in Norway, England, and Germany. In three separate matching procedures, patients were individually matched with respect to both dose equivalents and their respective propensity scores for ACEI treatment.

During a follow-up of 21,939 patient-years, 360 (49.5%), 337 (52.4%), and 1,119 (33.4%) patients died amongst those prescribed enalapril, lisinopril, and ramipril, respectively. In univariable analysis of the general sample, enalapril and lisinopril were both associated with higher mortality as compared with ramipril treatment (HR 1.46, 95% CI 1.30-1.65, p<0.001, and HR 1.38, CI 1.22-1.56, p<0.001, respectively). Patients prescribed enalapril or lisinopril had similar mortality (HR 1.06, 95% CI 0.92-1.24, p=0.41). However, there was no significant association between ACEI choice and all-cause mortality in any of the matched samples (HR 1.07, 95% CI 0.91-1.25, p=0.40; HR 1.12, 95% CI 0.96-1.32, p=0.16; and HR 1.08, HR 1.10, 95% CI 0.93-1.31, p=0.25 for enalapril vs. ramipril, lisinopril vs. ramipril, and enalapril vs. lisinopril, respectively). Results were confirmed in subgroup analyses with respect to age, sex, left ventricular ejection fraction, NYHA functional class, cause of HFrEF, rhythm, and systolic blood pressure.

Conclusion: Our results suggest that enalapril, lisinopril and ramipril are equally effective in the treatment of patients with HFrEF when given at equivalent doses. **Words:** 249

Key words: heart failure with reduced ejection fraction, angiotensin converting enzyme inhibitors, effectiveness, mortality

Introduction

Angiotensin converting-enzyme inhibitors (ACEIs) are recommended as first-line treatment for patients with heart failure with reduced ejection fraction (HFrEF), since randomized clinical trials have shown a reduction in all-cause mortality of 20–30% with ACEIs as compared with placebo (1-3). . However, only enalapril and lisinopril were tested in patients with chronic HFrEF (4-7). In contrast, other ACEIs were investigated in patients after myocardial infarction with differing degrees of left ventricular systolic dysfunction (8-10). Moreover, individual ACEIs differ in terms of their half-lives, bioavailability, lipophilicity, tissue penetration, bradykinin site selectivity, and routes of elimination (11). These distinct pharmacokinetic characteristics may result in varying effectiveness. To date, there are no large-scale trials comparing the effect of different ACEIs on survival in patients with HFrEF, and small head-to-head comparisons did not include the commonly used ACEIs enalapril, lisinopril, and ramipril (12-16). An early meta-analysis of randomized ACEI trials suggested a class effect of ACEIs (3), whereas a recently published network meta-analysis reported better survival with ramipril as compared with lisinopril or enalapril (17). However, patient characteristics varied significantly between trials and indirect between-trial comparisons may therefore not be reliable. In addition, the network meta-analysis included only 111 ramipril users with a short-term follow-up of 3 months, and it did not account for ACEI dosing. Thus, results should be interpreted with caution. Since head-to-head trials of ACEIs in patients with congestive heart failure are unlikely to be conducted, high-quality observational studies may be valuable to inform clinical decisions. We therefore compared the prognosis of patients prescribed enalapril, lisinopril or ramipril in a contemporary multicentre real-world cohort of patients with stable HFrEF from three European countries.

Methods

Databases

Patients' data were extracted from three different European heart failure databases: the Norwegian Heart Failure Registry, the Heart Failure Registry of the Department of Academic Cardiology, University of Hull, UK, and the Heart Failure Registry of the University of Heidelberg, Germany. Recruitment was prospective and continuous for each database and centre. All patients gave their written informed consent for data storage and evaluation. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committees.

The Norwegian Heart Failure Registry was initiated in October 2000 and patients were enrolled from the outpatient clinics of 27 recruiting hospitals well distributed in all regions of Norway ranging in size and scope from small community to large university hospitals. The participating centres recorded their data using a web-based database.

Patients who attended the community heart failure clinics of the University of Hull, UK, and the University of Heidelberg, Germany, for evaluation of heart failure were offered inclusion into the local heart failure registries. Since both university hospitals are providers of secondary and tertiary care, the registries reflect a broad representation of patients of their respective regions.

Patient selection and follow-up

All databases reflect all-comer cohorts. Patients were included after stabilization of both clinical status and medication. Patients were eligible for the study if they met **all** of the following criteria: a) attendance at the heart failure outpatient clinic of any of the participating hospitals, b) written informed consent for inclusion into the respective heart failure registry, c) diagnosis of HFrEF, and d) treatment with captopril, enalapril, lisinopril, ramipril, or trandolapril. In the complete database, however, captopril and trandolapril were hardly used

in any of the three participating registries. We therefore restricted to our analysis to enalapril, lisinopril and ramipril.

Medication was at the discretion of the referring physician. Target doses and dose equivalents for ACEIs were derived from ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (1). For example, daily doses of 10 mg ramipril, 20 mg enalapril or 20 mg lisinopril were considered as 100% dose equivalent, while 5 mg ramipril, 10 mg enalapril or 10 mg lisinopril were defined as 50% dose equivalent.

The diagnosis of heart failure was established according to guidelines on the basis of typical symptoms and signs associated with an objective abnormality of cardiac structure or function on echocardiography, cardiac magnetic resonance imaging, or left heart catheterisation (1). All included patients had a left ventricular ejection fraction (LVEF) <45%.

Baseline characteristics included medical history, physical examination, LVEF, blood count and chemistry, and medication. Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease (MDRD) formula (18).

Surviving patients were followed up for a minimum of six months. Determination of survival status and follow-up were performed by scheduled visits to the outpatient clinic, by telephone calls either to the patients' homes or to their physicians, or by electronic hospital records. For the purpose of the present analysis, patients were censored as "alive" at the date of this last contact. In addition, for the Norwegian Heart Failure Registry, mortality data were obtained at regular intervals from the National Statistics Bureau and no patient was lost to follow-up. All-cause mortality was the predefined endpoint of the study.

Statistical analysis

All tests are two-tailed and a *P*-value of less than 5% was regarded as being statistically significant. Variables are presented as mean ± standard deviation, median [interquartile range], or number [percentages (%)] as appropriate. Chi-squared tests were used to

compare frequencies. To test for significant differences between groups, the Kruskal-Wallis test and analysis of variance (ANOVA) tests were used where appropriate.

In order to prevent bias in further statistical analyses due to missing baseline values, we performed a multiple imputation analysis with n=100 repetitions using the Markov chain Monte Carlo method (MCMC). This procedure replaces each missing value with a set of plausible values that represent the uncertainty about the correct value for imputation.

Differences in event-free survival between patients treated with enalapril, lisinopril, or ramipril were analysed using Cox proportional hazard models and displayed using the Kaplan-Meier method for survival. To account for possible confounders, patients were matched with respect to ACEI treatment using pairwise multi-level propensity score matching as described below. Survival analyses were then repeated in matched cohorts.

Propensity score calculation and matching

Propensity scores were calculated as the single composite variable from a non-parsimonious multivariate logit-linked binary logistic regression of the baseline characteristics. The ACEI agent was the dependent variable (19). In a first step, propensity scores were calculated separately for “enalapril vs. ramipril”, “lisinopril vs. ramipril”, and “enalapril vs. lisinopril” as dependent variables. Propensity scores were derived from all baseline variables except for ACEI dose equivalent, haemoglobin, and NT-proBNP using the multiple imputed baseline data sets. Dose equivalent of the respective ACEI was not part of the propensity scores as it was used as a separate matching criterion. Haemoglobin and NT-proBNP were excluded due to a large number of missing variables. The logits of the probability of receiving a certain ACEI according to the respective propensity scores formed the basis of three separate matching procedures.

Patients were individually matched for both the propensity of receiving a particular ACEI and their dose equivalents. Each matching procedure was performed in two steps: First, calliper matching of the propensity score was applied with calliper size predefined as 0.2 of the

standard deviation of the total sample. In a one-pass procedure starting with a given patient receiving a certain ACEI (e.g. enalapril), the closest match of a patient receiving a different ACEI (e.g. ramipril) was identified. Second, dose equivalents for the ACEIs were compared. If doses were equivalent or varied ≤10%, the pair of patients was retained for analysis and removed from the total sample to allow for the next matching cycle to take place. If doses varied >10%, the pair was rejected. Then the first step of the matching process was repeated to identify the next closest match to the given enalapril patient of the failed match according to the propensity score. If a further patient on ramipril was thus identified, the second step was repeated. If no match according to the propensity score AND dose equivalent could be identified, the enalapril patient was removed from the total sample and the matching cycle started with the next ramipril patient.

The matching procedures of patients treated with enalapril vs. lisinopril and lisinopril vs. ramipril were performed analogously. Owing to this statistical design, the matched patients included in each drug cohort differed between comparisons.

Bias reduction, balance and sensitivity analysis

The balance of baseline covariates before and after matching was assessed using standardised differences (20). In addition, Chi-squared test, Mann-Whitney-U test, and student's t-test were used to test for differences in baseline variables after matching. As a sensitivity analysis to univariable survival analyses in the matched samples, we performed multivariable Cox regression analyses including significant covariates in the matched samples. Furthermore, we performed a multivariable Cox regression analysis in the general sample including covariates that were significant in univariable analyses. Finally, we conducted a formal sensitivity analysis to quantify the degree of a hidden bias that would need to be present to invalidate our main conclusions following the method suggested by Love (21).

Subgroups

Analyses were repeated in pre-specified subgroups of the matched samples with respect to age (above vs. below median), sex, LVEF (≤35% vs. >35%), NYHA functional class (I/II vs. III/IV), rhythm (sinus rhythm yes vs. no), cause of heart failure (ischaemic vs. non-ischaemic), and systolic blood pressure (≤120mmHg vs. >120mmHg). Interaction terms were calculated for each of the predefined subgroups in the propensity matched samples.

Results

We identified 8,005 patients with HFrEF in the three heart failure databases. Figure 1 shows the composition and selection flow with respect to the different ACEIs in our study population. Of 4,723 patients who met the inclusion criteria outlined above, 3,074 patients were from Norway, 837 patients were from Germany, and 812 patients were from England.

Enalapril was prescribed for 727 patients (15.4%) with a median dose of 20 (10-20)mg/d (equivalent to 100 (50-100)% of target dose), lisinopril for 643 patients (13.6%) with a median dose of 20 (10-20)mg/d (equivalent to 100 (50-100)% of target dose), and ramipril for 3,353 patients with a median dose of 10 (5-10)mg/d (equivalent to 100 (50-100)% of target dose).

Baseline characteristics of HFrEF patients differed with respect to ACEI treatment for a number of variables (*table 1*). Overall, patients receiving ramipril were younger and more likely to have NYHA functional class I or II symptoms than those on enalapril and lisinopril. NT-proBNP levels were lower in the ramipril group, whereas LVEF was similar in all three treatment groups. In patients using lisinopril, systolic blood pressure was significantly higher as compared to patients on enalapril or ramipril.

Total follow-up was 263,265 patient-months (21,939 patient-years) with a median follow-up duration of 50 (27-80) months. For enalapril, median follow-up was 50 (24-80) months, whereas it was 55 (28-90) months and 49 (27-77) months for lisinopril and ramipril,

respectively. During that time 1,816 (38.5%) patients died: 360 (49.5%) on enalapril, 337 (52.4%) on lisinopril, and 1,119 (33.4%) on ramipril.

In univariable analysis of the overall cohort, patients prescribed enalapril and lisinopril both had higher mortality when compared with those prescribed ramipril (HR 1.46, 95% CI 1.30-1.65, p<0.001, and HR 1.38, CI 1.22-1.56, p<0.001, respectively). Survival on enalapril was similar to that on lisinopril (HR 1.06, 95% CI 0.92-1.24, p=0.41). Kaplan–Meier curves for 10-year survival with respect to ACEI treatment are shown in *figure 2*.

The matching procedures identified 688, 622 and 538 pairs of patients with similar dose-equivalent for each of the three comparisons (enalapril vs. ramipril, lisinopril vs. ramipril and enalapril vs. lisinopril). Of these, 639 (46%), 589 (47%), and 551 (51%) patients died during follow-up, respectively. Each of the propensity score matching procedures significantly reduced standardized differences below 10% in the absolute values for most observed covariates, demonstrating a substantial improvement in the covariate balance across the treatment groups (*figure 3 a) and b)*). However, matched patients treated with enalapril or ramipril differed with respect to NT-proBNP levels (1,065 (482-2,170) ng/l vs.1,311 (604-2,881) ng/l, p=0.03) and loop diuretic dose (40 (40-80) mg vs. 40 (20-80) mg, p=0.007), while matched patients using enalapril or lisinopril varied with respect to haemoglobin concentrations (13.5±1.6 g/dl vs. 13.8±1.4 g/dl, p=0.02). Detailed descriptions of the matched samples are available in the supplementary material online (Tables 2-4).

Univariable Cox proportional hazard analyses did not find any significant association between the particular ACEIs prescribed and all-cause mortality in any of the matched samples (enalapril vs. ramipril, HR 1.07, 95% CI 0.91-1.25, p=0.40; lisinopril vs. ramipril, HR 1.12, 95% CI 0.96-1.32, p=0.16; enalapril vs. lisinopril, HR 1.10, 95% CI 0.93-1.31, p=0.25). Results were confirmed after adjusting for covariates in the matched samples (HR 1.03, 95% CI 0.78-1.37, p=0.84 for enalapril versus ramipril, and HR 0.97, 95% CI 0.74-1.26, P=0.81 for enalapril versus lisinopril, respectively). The Kaplan–Meier curves for survival of matched HFrEF patients with respect to ACEI treatment are presented in *figures 4-6.*

Similarly, we found no relationship between the type of ACEI and all-cause mortality in multivariable Cox regression analysis of the general sample including significant variables from univariable analyses (HR 1.19, 95% CI 0.79-1.79, p=0.41 for enalapril versus lisinopril, HR 1.31, 95% CI 0.97-1.77, p=0.08 for enalapril versus ramipril, and HR 1.13, 95% CI 0.81-1.57, P=0.48 for lisinopril versus ramipril, respectively),

Subgroup analyses confirmed that none of the ACEIs was superior to one of the others. The relevant plot is shown in *figure 7*.

The formal sensitivity analyses indicate only a small residual bias. The respective Γ-values were 0.73, 0.64, and 0.80 for enalapril vs. ramipril, lisinopril vs. ramipril, and enalapril vs. lisinopril (no residual bias at Γ=1.0). This means that in order to attribute a possible survival benefit to an unobserved covariate rather than the receipt of e.g. enalapril (vs. lisinopril), that unobserved covariate would only need to produce a 20% increase in the odds of receipt of enalapril while being a weak predictor of all-cause mortality.

Discussion

In this European multicentre cohort study of outpatients with stable HFrEF, we analysed the association of treatment with the 3 ACEIs enalapril, lisinopril and ramipril and survival. Our main findings are that

- patient characteristics differed significantly between treatment groups. Ramipril users were younger, had lower NT-proBNP levels and were in a lower NYHA functional class that enalapril and lisinopril users.
- consequently, treatment with ramipril was superior to enalapril and lisinopril therapy in univariable analysis of the general sample.
- after controlling for confounders and ACEI dose, no difference in survival was noted between the 3 individual ACEIs.
- results were consistent through a range of important subgroups.

Although substantial evidence exists to support the use of ACEIs in patients with HFrEF, there is little evidence and conflicting literature on the relative effectiveness of different ACEIs in everyday use (22-27).

Our study contrasts to other observational studies suggesting a different effectiveness of individual ACEIs in heart failure patients (24-27). Two large retrospective analyses from Canadian administrative databases including elderly patients admitted for heart failure (24) and after myocardial infarction (25) reported better outcomes with ramipril as compared with enalapril. In addition, in data from almost 140,000 patients with heart failure from the American Veterans Health Administration (26, 27), lisinopril was associated with lower mortality than captopril, whereas enalapril was equally effective as captopril (26). Unfortunately, no comparison was performed between lisinopril and enalapril, and ramipril was not included in the analysis. An important limitation of both the Canadian and the American studies, however, is the lack of information on relevant patient characteristics such as LVEF, type of heart failure, and NYHA functional class. The results may accordingly be susceptible to confounding by indication and severity of heart failure. Likewise, we found better survival in ramipril users in univariable analyses of the general sample. After controlling for important covariates including LVEF, NYHA functional class and NT-proBNP, however, outcomes were similar between treatments. Then again, another Canadian study of 6,753 patients with newly diagnosed heart failure found no significant differences between enalapril, lisinopril, and ramipril in terms of heart failure effectiveness (23). Similarly, a recent analysis of 7,291 patients with HFrEF from the Danish Heart Failure Registry suggested an equal reduction in all-cause mortality with the use of enalapril as compared with ramipril (22).

Our study supports the results from the Danish study while paying particular attention on equivalent dosing of ACEIs. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial reported significantly better outcomes in patients treated with high doses of lisinopril as compared with low-dose users (7). Therefore, inclusion of ACEI dosing in the comparison of different ACEIs in patients with HFrEF seems crucial.

In agreement with the Danish cohort study (22), we confirmed equal effectiveness of ACEIs in subgroup analyses with respect to age, sex, LVEF, NYHA functional class, and cause of heart failure. In addition, outcomes were verified in subgroups of patients according to heart rhythm and systolic blood pressure. As there are no other studies on the relative effectiveness of ACEIs providing subgroup analyses, our study expands the available evidence.

Limitations

As with any non-randomized, observational design, the present study may be subject to unmeasured confounders. Sensitivity analyses cannot prove or rule out the presence of such an unmeasured confounder. However, our data result from comprehensive outpatient databases with continuous, prospective inclusion and close surveillance. The detailed characterization of patients allows consideration of various potential confounders through the use of comprehensive propensity score and multivariable Cox regression models. The large sample size and prospective inclusion of patients from three European countries are obvious strengths of the present study. The results are therefore likely to be generalizable to other HFrEF populations. We observed substantial differences in patient characteristics between countries, with the majority of patients being recruited in Norway. However, as patient characteristics were used for propensity score calculation and matching, we expect that this should not have an impact on our results in the matched cohorts. In addition, country did not have a significant, independent impact on survival when entered as a covariate in multivariable Cox regression analysis ($p=0.86$). We further cannot comment on the specific reasons for selection of a particular ACEI, nor on medication adherence. In addition, our data do not allow identification of patients who either switched from one ACEI to another or changed ACEI dosing during follow-up. As inclusion into the analyses of our study was performed after stabilization of both clinical status and medication in an ambulatory setting, however, this may reduce the necessity for further modulation of ACEI treatment.

From this observational study, we can infer that there is no association between the ACEI prescribed and mortality but we cannot be sure that the lack of observed difference truly reflects similar benefit. Ideally, our results should be confirmed in a large-scale, randomized head-to-head comparison of ACEIs. Given the required sample size and associated costs, such a trial may never be done.

Conclusion

In this European multicentre cohort study of patients with HFrEF, we found no difference in all-cause mortality for patients treated with enalapril, lisinopril or ramipril. The results were consistent in subgroups with respect to age, sex, NYHA functional class, LVEF, sinus rhythm, cause of heart failure, and blood pressure. These findings support the assumption of a class effect among the 3 ACEIs on mortality in patients with HFrEF.

Conflict of Interest: Dr. Cleland reports grants and personal fees from Amgen, Novartis, Servier, and Stealth outside the submitted work. Dr. Katus reports personal fees from AstraZeneca, Bayer Vital, Roche Diagnostics, and Daiichi Sankyo outside the submitted work.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129-200.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016.

3. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273(18):1450-6.

4. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316(23):1429-35.

5. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325(5):293-302.

6. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. N Engl J Med. 1992;327(10):685-91.

7. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor,

lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100(23):2312-8.

8. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327(10):669-77.

9. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342(8875):821-8.

10. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333(25):1670-6.

11. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation. 1998;97(14):1411-20.

12. Gavazzi A, Marioni R, Campana C, Montemartini C. Comparative trial of quinapril versus captopril in mild to moderate congestive heart failure. Quinapril/Captopril Congestive Heart Failure Study Group. J Hypertens Suppl. 1994;12(4):S89-93.

13. Bach R, Zardini P. Long-acting angiotensin-converting enzyme inhibition: once-daily lisinopril versus twice-daily captopril in mild-to-moderate heart failure. Am J Cardiol. 1992;70(10):70C-7C.

14. Borghi C, Ambrosioni E, Survival of Myocardial Infarction Long-term Evaluation-2 Working P. Double-blind comparison between zofenopril and lisinopril in patients with acute myocardial infarction: results of the Survival of Myocardial Infarction Long-term Evaluation-2 (SMILE-2) study. Am Heart J. 2003;145(1):80-7.

15. Foy SG, Crozier IG, Turner JG, Richards AM, Frampton CM, Nicholls MG, et al. Comparison of enalapril versus captopril on left ventricular function and survival three months after acute myocardial infarction (the "PRACTICAL" study). Am J Cardiol. 1994;73(16):1180-6.

16. Giles TD, Katz R, Sullivan JM, Wolfson P, Haugland M, Kirlin P, et al. Short- and long-acting angiotensin-converting enzyme inhibitors: a randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. The Multicenter Lisinopril-Captopril Congestive Heart Failure Study Group. J Am Coll Cardiol. 1989;13(6):1240-7.

17. Sun W, Zhang H, Guo J, Zhang X, Zhang L, Li C, et al. Comparison of the Efficacy and Safety of Different ACE Inhibitors in Patients With Chronic Heart Failure: A PRISMA-Compliant Network Meta-Analysis. Medicine (Baltimore). 2016;95(6):e2554.

18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals of internal medicine. 1999;130(6):461-70.

19. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J. 2009;51(1):171-84.

20. Rosenbaum PR. Observational studies. 2 ed. Heidelberg, Berlin: Springer; 2002.

21. Love TE. Spreadsheet-based sensitivity analysis calculations for matched samples. Case Western Reserve University.: Center for Health Care Research & Policy; 2008 [Available from: http://www.chrp.org/propensity.

22. Svanstrom H, Pasternak B, Melbye M, Hviid A. Use of different types of angiotensin converting enzyme inhibitors and mortality in systolic heart failure. Int J Cardiol. 2015;182:90-6.

23. Tu K, Mamdani M, Kopp A, Lee D. Comparison of angiotensin-converting enzyme inhibitors in the treatment of congestive heart failure. Am J Cardiol. 2005;95(2):283-6.

24. Pilote L, Abrahamowicz M, Eisenberg M, Humphries K, Behlouli H, Tu JV. Effect of different angiotensin-converting-enzyme inhibitors on mortality among elderly patients with congestive heart failure. CMAJ. 2008;178(10):1303-11.

25. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? Ann Intern Med. 2004;141(2):102-12.

26. Chitnis AS, Aparasu RR, Chen H, Johnson ML. Effect of certain angiotensin-converting enzyme inhibitors on mortality in heart failure: a multiple-propensity analysis. Res Social Adm Pharm. 2012;8(2):145-56.

27. Chitnis AS, Aparasu RR, Chen H, Johnson ML. Comparative effectiveness of different angiotensin-converting enzyme inhibitors on the risk of hospitalization in patients with heart failure. J Comp Eff Res. 2012;1(2):195-206.

Figure legends

Figure 1:

Title: Inclusion of ACEI users in study cohort.

Legend: ACEI, angiotensin converting enzyme inhibitor

Figure 2:

Title: Kaplan–Meier curves for 10-year survival for hospital outpatients with chronic heart failure with reduced ejection fraction receiving enalapril, lisinopril, and ramipril, respectively.

Figure 3 a) and b):

Title: Absolute standardized differences before (a) and after (b) propensity score matching comparing covariate values for hospital outpatients with chronic heart failure with reduced ejection fraction receiving enalapril vs. ramipril, lisonopril vs. ramipril, and enalapril vs. lisinopril, respectively.

Legend: BMI, body mass index; NYHA, New York Heart Association functional class; OPD, obstructive pulmonary disease; aHT, arterial hypertension; BPsys, systolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; ACEI, angiotensin converting enzyme.

Figure 4:

Title: Kaplan–Meier curves for 10-year survival regarding all-cause mortality in the propensity and dose-equivalent matched cohort for hospital outpatients with chronic heart failure with reduced ejection fraction receiving enalapril or ramipril.

Figure 5:

Title: Kaplan–Meier curves for 10-year survival regarding all-cause mortality in the propensity and dose-equivalent matched cohort for hospital outpatients with chronic heart failure with reduced ejection fraction receiving lisinopril or ramipril.

Figure 6:

Title: Kaplan–Meier curves for 10-year survival regarding all-cause mortality in the propensity and dose-equivalent matched cohort for hospital outpatients with chronic heart failure with reduced ejection fraction receiving enalapril or lisinopril.

Figure 7:

Title: Cox regression analyses for all-cause mortality regarding ACEI use in the predefined subgroups for the propensity score matched cohorts

Legend: RRsys, systolic blood pressure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class. **P* for interaction refers to subgroups of each propensity matched sample.

Table 1

Table 1: Baseline characteristics of CHF patients with respect to ACEI treatment

	All patients n=4,723	**Enalapril n=727**	**Lisinopril n=643**	**Ramipril n=3,353**	**P-value**	**P-value***
Age, *y [n=4,723]*	67±13	68±12	70±12	66±13	*<0.001*	*<0.001*
Men, *n(%) [n=4,723]*	3,609 (76.4)	553 (76.1)	480 (74.7)	2,576 (76.8)	0.48	*0.02*
BMI, *kg/m² [n=4,375]*	27.0±5.1	27.2±5.2	26.9±5.0	27.0±5.1	0.49	*<0.001*
Heart Failure Registry *[n=4,723]*						n.a.
Norway, *n(%)*	3,074 (65.1)	515 (70.8)	456 (70.9)	2,105 (62.8)		
Heidelberg, *n(%)*	837 (17.7)	114 (15.7)	50 (7.8)	673 (20.1)		
Hull, *n(%)*	812 (17.2)	98 (13.5)	139 (21.6)	575 (17.1)		
Cause of HFrEF *[n=4,723]*					0.49	*<0.001*
Ischaemic, *n(%)*	2,810 (59.5)	447 (61.5)	379 (58.9)	1,984 (59.2)		
Non-ischaemic, *n(%)*	1,913 (40.5)	280 (38.5)	264 (41.1)	1,369 (40.8)		
NYHA, *n(%) [n=4,656]*					*<0.001*	*<0.001*
I	823 (17.7)	76 (10.6)	77 (12.2)	670 (20.2)		
II	2,469 (53.0)	393 (54.7)	329 (52.2)	1,747 (52.7)		
III	1,332 (28.6)	245 (34.1)	214 (34.0)	873 (26.4)		
IV	37 (0.8)	4 (0.6)	10 (1.6)	23 (0.7)		
LVEF, *% [n=4,147]*	30±9	29±9	30±9	30±8	0.09	*<0.001*
BPsys, *mmHg [n=4,674]*	123±21	123±21	126±23	122±21	*0.002*	*<0.001*
Sinus rhythm, *n(%) [n=4,723]*	2,633 (55.7)	384 (52.8)	339 (52.7)	1,910 (57.0)	*0.03*	*<0.001*
HR, *1/min [n=4,670]*	69±13	68±13	70±14	68±13	0.12	*<0.001*
NT-proBNP, *pg/mL [n=2,103]*	1,012 (369-2,399)	1,069 (483-2,248)	1,166 (497-2,636)	949 (338-2,392)	*0.01*	*<0.001*

Creatinine, *µmol/L [n=4,590]*	96 (81-118)	102 (83-126)	102 (85-128)	94 (80-115)	*<0.001*	*<0.001*
eGFR, *mL/min/1.73m²* *[n=4,590]*	65 (50-83)	61 (46-80)	60 (46-76)	67 (52-85)	*<0.001*	*<0.001*
Sodium, *mmol/L* *[n=5,572]*	140 ± 3	139 ± 3	140 ± 3	140 ± 3	0.056	*<0.001*
Potassium, *mmol/L* *[n=4,572]*	4.4±0.4	4.5±0.5	4.4±0.4	4.4±0.4	*0.001*	*<0.001*
Haemoglobin, *g/dL* *[n=2,654]*	13.8 ± 1.5	13.6 ± 1.6	13.8 ± 1.5	13.8 ± 1.5	*0.01*	0.29
Comorbidities, *n(%)*						
OPD *[n=4,723]*	590 (12.5)	88 (12.1)	72 (11.2)	430 (12.8)	0.49	*<0.001*
aHT *[n=4,723]*	1,739 (36.8)	282 (38.8)	226 (35.1)	1,231 (3.7)	0.37	*<0.001*
Hyperlipidaemia *[n=4,723]*	2,265 (48.0)	359 (49.4)	280 (43.5)	1,626 (48.5)	0.06	*<0.001*
Smoker *[n=4,723]*	763 (16.1)	113 (15.5)	104 (16.2)	546 (16.3)	*<0.001*	*<0.001*
Stroke *[n=4,723]*	317 (6.7)	65 (8.9)	47 (7.3)	205 (6.1)	*0.007*	*<0.001*
PVD *[n=4,723]*	294 (6.2)	47 (6.5)	29 (4.5)	218 (6.5)	*0.03*	*<0.001*
Diabetes *[n=4,723]*	918 (19.1)	162 (22.3)	115 (17.9)	641 (19.4)	0.08	*<0.001*
Treatment						
ACEI dose equivalent, *%* *[n=4,723]*	100 (50-100) [79±32]	100 (50-100) [81±37]	100 (50-100) [73±37]	100 (50-100) [80±30]	*<0.001*	*<0.001*
Beta-blocker, *n(%)* *[n=4,723]*	4,143 (87.7)	610 (83.9)	528 (82.1)	3,005 (89.6)	*<0.001*	*<0.001*
Beta-blocker dose equivalent, *%*	53 (26-100) [63±36]	53 (26-100) [62±35]	53 (26-100) [68±36]	53 (26-100) [63±36]	0.80	*<0.001*

[n=4,143]						
ARB, *n(%) [n=4,723]*	176 (3.7)	26 (3.6)	15 (2.3)	135 (4.0)	0.11	*<0.001*
MRA, *n(%) [n=4,717]*	1,506 (31.9)	226 (31.2)	167 (26.0)	1,113 (33.2)	*0.001*	*<0.001*
Loop diuretic, *n(%) [n=4,723]*	3,524 (74.6)	595 (81.8)	517 (80.4)	2,412 (71.9)	*<0.001*	*<0.001*
Loop diuretic dose*, mg furosemide [n=3,524]*	40 (20-80)	40 (40-80)	40 (40-80)	40 (20-80)	*<0.001*	*<0.001*
Aspirin, *n(%) [n=4,723]*	1,905 (40.3)	257 (35.4)	224 (34.8)	1,424 (42.5)	*<0.001*	*<0.001*
Statin, *n(%) [n=4,723]*	2,548 (53.9)	385 (53.0)	336 (52.3)	1,827 (54.5)	0.49	*<0.001*

Values shown are mean±SD or median (interquartile range). P-values <0.05 are written in italics. P-value* refers to comparisons of unadjusted variables between countries. n, number; ACEI, angiotensin converting enzyme inhibitor; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BPsys, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; OPD, obstructive pulmonary disease; aHT, arterial hypertension; PVD, peripheral vascular disease; ARB, angiotensin receptor antagonist; MRA, mineralocorticoid receptor antagonist. Dose equivalent represent percentage achieved of the individual drug with respect to the guideline recommended target dose.

Table 2: Baseline characteristics of matched CHF patients treated with enalapril or ramipril

	Enalapril n=688	**Ramipril n=688**	**P-value**
Age, *y*	68±13	68±13	0.74
Men, *n(%)*	525 (76.3)	514 (74.7)	0.49
BMI, *kg/m²*	27.1±5.2	27.3±5.6	0.68
Cause of HFrEF			0.96
Ischaemic, *n(%)*	422 (61.4)	422 (61.4)	
Non-ischaemic, *n(%)*	266 (38.6)	266 (38.6)	
NYHA, *n(%)*			0.59
I	74 (10.8)	87 (12.6)	
II	369 (53.6)	369 (53.6)	
III	233 (33.9)	220 (32.0)	
IV	3 (0.4)	5 (0.7)	
LVEF, *%*	29±9	29±9	0.99
BPsys, *mmHg*	122±21	122±21	0.99
Sinus rhythm, *n(%)*	368 (53.5)	353 (51.3)	0.42
HR, 1/min	68±13	69±13	0.50
NT-proBNP, *pg/mL*	1,065 (482-2,170)	1,311 (604-2,881)	*0.03*
Creatinine, *µmol/L*	102 (83-125)	99 (82-123)	0.93
eGFR, *mL/min/1.73m²*	62 (47-80)	62 (47-80)	0.68
Sodium, *mmol/L*	139±3	139±3	0.34
Potassium, *mmol/L*	4.5±0.4	4.5±0.5	0.23
Haemoglobin, *g/dL*	13.6 ± 1.6	13.7 ± 1.7	0.20
Comorbidities, *n(%)*			
OPD	82 (11.9)	73 (10.6)	0.44

aHT	262 (38.1)	269 (39.1)	0.70
Hyperlipidaemia	345 (50.1)	339 (49.3)	0.75
Smoker	109 (15.8)	101 (14.7)	0.55
Stroke	61 (8.9)	54 (7.8)	0.50
PVD	47 (6.8)	37 (5.4)	0.26
Diabetes	152 (22.1)	165 (24.0)	0.41
Treatment			
ACEI dose equivalent, *%*	100 (50-100)	100 (50-100)	1.00
Beta-blocker, *n(%)*	585 (85.0)	576 (83.7)	0.50
Beta-blocker dose equivalent, *%*	53 (26-100)	53 (26-100)	0.62
ARB, *n(%)*	25 (3.6)	33 (4.8)	0.28
MRA, *n(%)*	212 (30.8)	224 (32.6)	0.22
Loop diuretic, *n(%)*	558 (81.1)	540 (78.5)	0.23
Loop diuretic dose*, mg furosemide*	40 (40-80)	40 (20-80)	*0.007*
Aspirin, *n(%)*	249 (36.2)	249 (36.2)	1.00
Statin, *n(%)*	352 (52.6)	370 (53.8)	0.67

Values shown are mean±SD or median (interquartile range). P-values <0.05 are written in italics. n, number; ACEI, angiotensin converting enzyme inhibitor; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BPsys, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; OPD, obstructive pulmonary disease; aHT, arterial hypertension; PVD, peripheral vascular disease; ARB, angiotensin receptor antagonist; MRA, mineralocorticoid receptor antagonist. Dose equivalent represent percentage achieved of the individual drug with respect to the guideline recommended target dose.

Table 3: Baseline characteristics of matched CHF patients treated with lisinopril or ramipril

	Lisinopril n=622	**Ramipril n=622**	**P-value**
Age, *y*	70±12	70±12	0.57
Men, *n(%)*	464 (74.6)	456 (73.3)	0.61
BMI, *kg/m²*	27.1±5.4	26.9±5.0	0.41
Cause of HFrEF			0.57
Ischaemic, *n(%)*	360 (57.9)	371 (59.6)	
Non-ischaemic, *n(%)*	262 (42.1)	251 (40.4)	
NYHA, *n(%)*			0.99
I	74 (12.2)	72 (11.7)	
II	315 (51.7)	318 (51.6)	
III	210 (34.5)	215 (34.9)	
IV	10 (1.6)	11 (1.8)	
LVEF, *%*	30±9	30±8	0.92
BPsys, *mmHg*	125±22	125±22	0.82
Sinus rhythm, *n(%)*	332 (53.4)	331 (53.2)	0.96
HR, 1/min	70±14	70±14	0.75
NT-proBNP, *pg/mL*	1,178 (491-2,778)	1,481 (646-3,637)	0.12
Creatinine, *µmol/L*	102 (84-127)	102 (85-127)	0.58
eGFR, *mL/min/1.73m²*	59 (46-76)	60 (46-75)	0.76
Sodium, *mmol/L*	140±3	140±3	0.23
Potassium, *mmol/L*	4.4±0.4	4.4±0.5	0.31
Haemoglobin, *g/dL*	13.8±1.5	13.6±1.7	0.13
Comorbidities, *n(%)*			
OPD	72 (11.6)	66 (10.6)	0.59

aHT	219 (35.2)	220 (35.4)	0.95
Hyperlipidaemia	271 (43.6)	255 (41.0)	0.36
Smoker	100 (16.1)	82 (13.2)	0.15
Stroke	45 (7.2)	46 (7.4)	0.92
PVD	29 (4.7)	26 (4.2)	0.68
Diabetes	111 (17.8)	108 (17.4)	0.82
Treatment			
ACEI dose equivalent, *%*	75 (50-100)	75 (50-100)	0.99
Beta-blocker, *n(%)*	512 (82.3)	514 (82.6)	0.88
Beta-blocker dose equivalent, *%*	53 (26-100)	53 (26-100)	0.19
ARB, *n(%)*	14 (2.3)	12 (1.9)	0.69
MRA, *n(%)*	162 (26.0)	155 (24.9)	0.13
Loop diuretic, *n(%)*	502 (80.7)	495 (79.6)	0.62
Loop diuretic dose*, mg furosemide*	40 (30-80)	40 (40-80)	0.06
Aspirin, *n(%)*	218 (35.0)	211 (33.9)	0.68
Statin, *n(%)*	328 (52.7)	322 (51.8)	0.73

Values shown are mean±SD or median (interquartile range). P-values <0.05 are written in italics. n, number; ACEI, angiotensin converting enzyme inhibitor; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BPsys, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; OPD, obstructive pulmonary disease; aHT, arterial hypertension; PVD, peripheral vascular disease; ARB, angiotensin receptor antagonist; MRA, mineralocorticoid receptor antagonist. Dose equivalent represent percentage achieved of the individual drug with respect to the guideline recommended target dose.

Table 4: Baseline characteristics of matched CHF patients treated with enalapril or lisinopril.

	Enalapril n=538	**Lisinopril n=538**	**P-value**
Age, *y*	69±12	69±12	0.71
Men, *n(%)*	408 (75.8)	409 (76.0)	0.94
BMI, *kg/m²*	26.9±5.1	27.1±5.0	0.63
Cause of HFrEF			0.46
Ischaemic, *n(%)*	324 (60.2)	312 (58.0)	
Non-ischaemic, *n(%)*	214 (39.8)	226 (42.0)	
NYHA, *n(%)*			0.66
I	55 (10.3)	71 (13.5)	
II	285 (53.4)	281 (53.3)	
III	190 (35.6)	170 (32.3)	
IV	4 (0.7)	5 (0.9)	
LVEF, *%*	30±9	30±9	0.75
BPsys, *mmHg*	124±21	125±22	0.44
Sinus rhythm, *n(%)*	286 (53.2)	281 (52.2)	0.76
HR, 1/min	69±12	68±13	0.71
NT-proBNP, *pg/mL*	1,171 (448-2,300)	1,099 (435-2,468)	0.51
Creatinine, *µmol/L*	104 (85-127)	102 (85-127)	0.40
eGFR, *mL/min/1.73m²*	59 (45-76)	61 (47-78)	0.42
Sodium, *mmol/L*	139±4	140±3	0.89
Potassium, *mmol/L*	4.5±0.4	4.5±0.4	0.65
Haemoglobin, *g/dL*	13.5±1.6	13.8±1.4	*0.02*
Comorbidities, *n(%)*			
OPD	62 (11.5)	61 (11.9)	0.85

aHT	195 (36.2)	198 (36.8)	0.85
Hyperlipidaemia	248 (46.1)	252 (46.8)	0.81
Smoker	86 (16.0)	86 (16.0)	1.00
Stroke	45 (8.4)	44 (8.2)	0.92
PVD	28 (5.2)	26 (4.8)	0.78
Diabetes	106 (19.7)	100 (18.6)	0.64
Treatment			
ACEI dose equivalent, *%*	100 (50-100)	100 (50-100)	0.99
Beta-blocker, *n(%)*	444 (82.5)	447 (83.1)	0.81
Beta-blocker dose equivalent, *%*	53 (26-100)	53 (39-100)	0.15
ARB, *n(%)*	18 (3.3)	13 (2.4)	0.36
MRA, *n(%)*	150 (27.9)	150 (27.9)	0.85
Loop diuretic, *n(%)*	435 (80.9)	437 (81.2)	0.88
Loop diuretic dose*, mg furosemide*	40 (40-80)	40 (40-80)	0.33
Aspirin, *n(%)*	184 (34.2)	193 (35.9)	0.57
Statin, *n(%)*	281 (52.2)	288 (53.5)	0.67

Values shown are mean±SD or median (interquartile range). P-values <0.05 are written in italics. n, number; ACEI, angiotensin converting enzyme inhibitor; BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; BPsys, systolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; OPD, obstructive pulmonary disease; aHT, arterial hypertension; PVD, peripheral vascular disease; ARB, angiotensin receptor antagonist; MRA, mineralocorticoid receptor antagonist. Dose equivalent represent percentage achieved of the individual drug with respect to the guideline recommended target dose.

Figure 1

Click here to download Figure Flowchart Patienteneinschluss.jpg

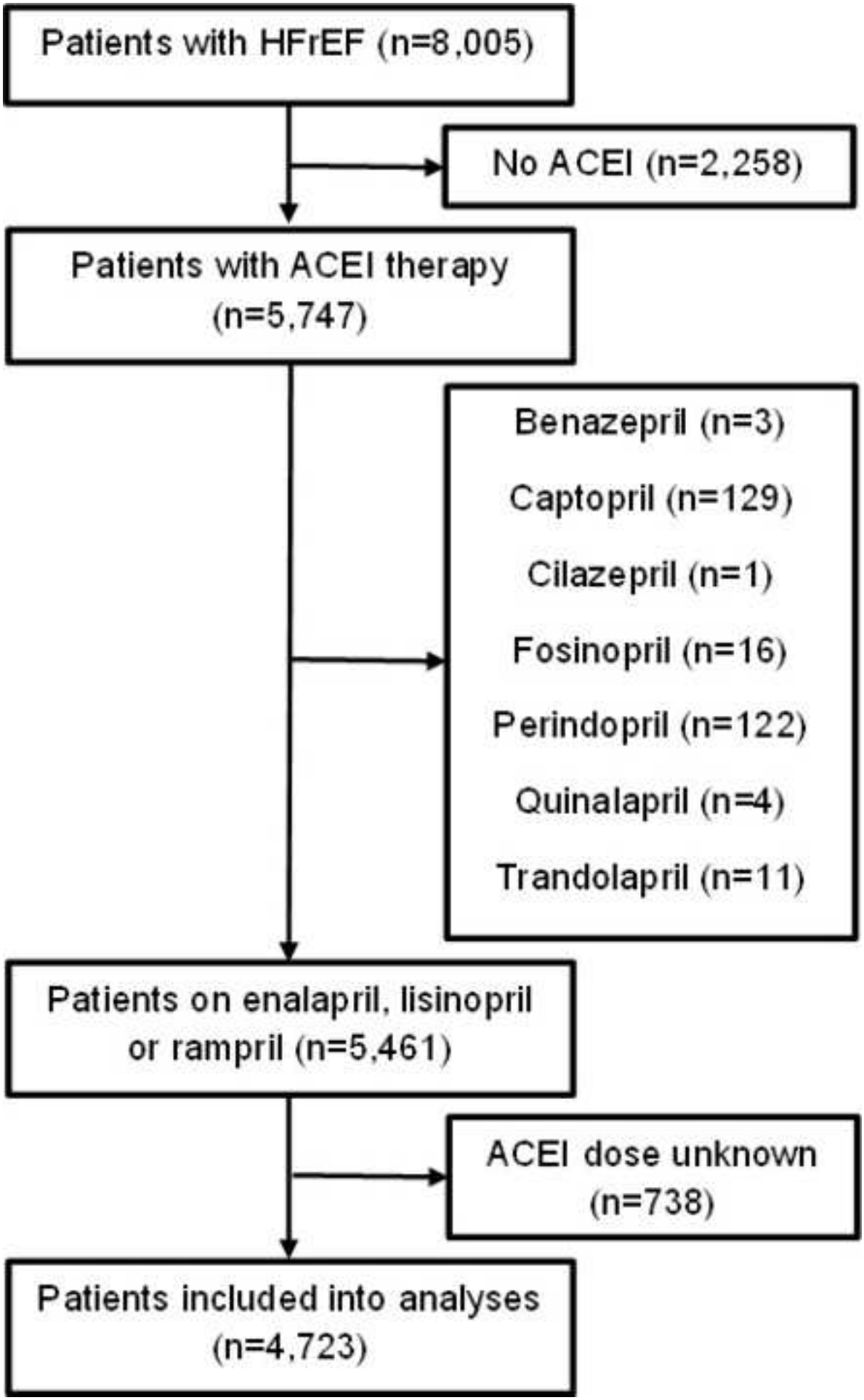

Figure 2

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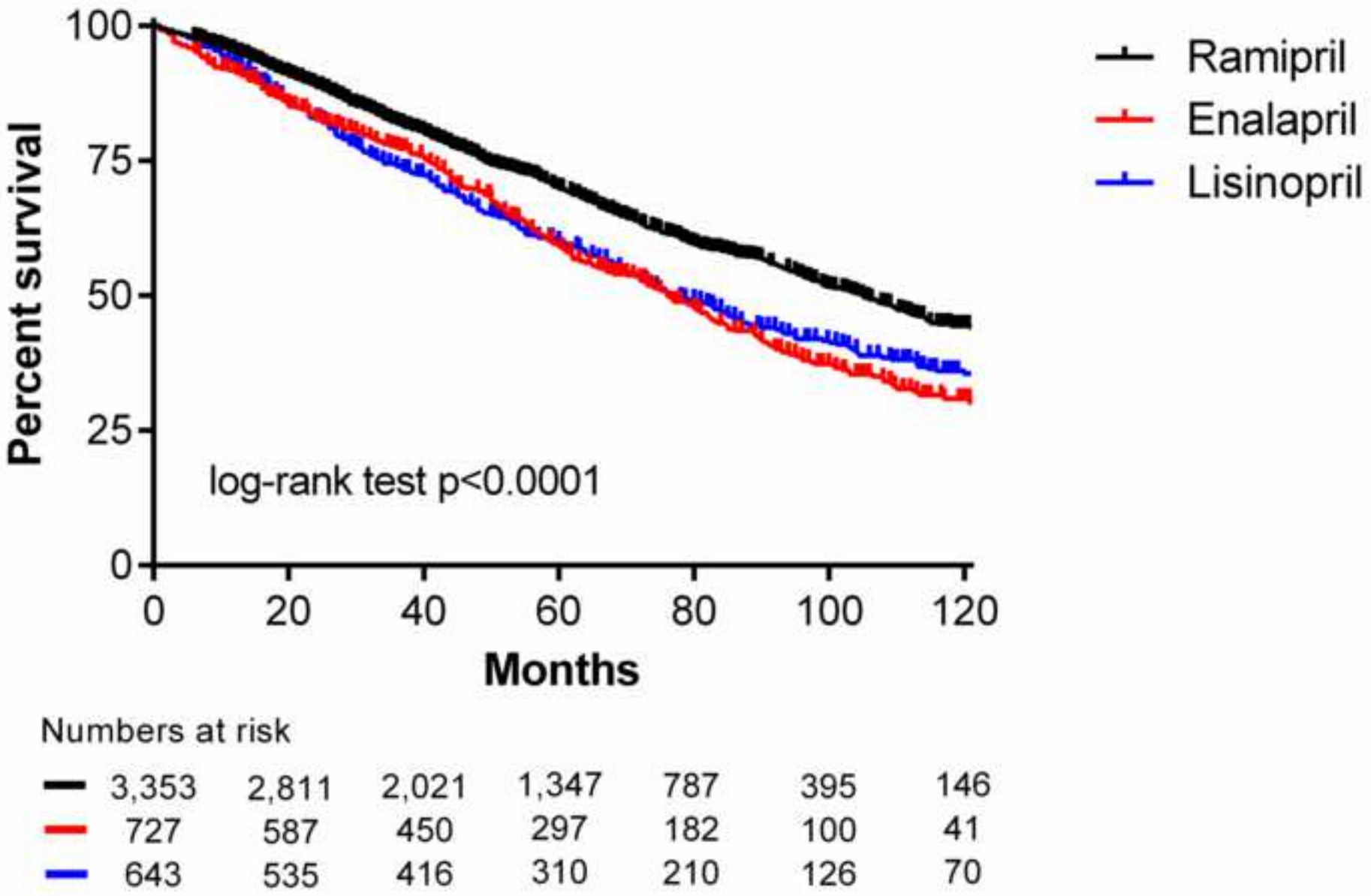

Figure 3 a)

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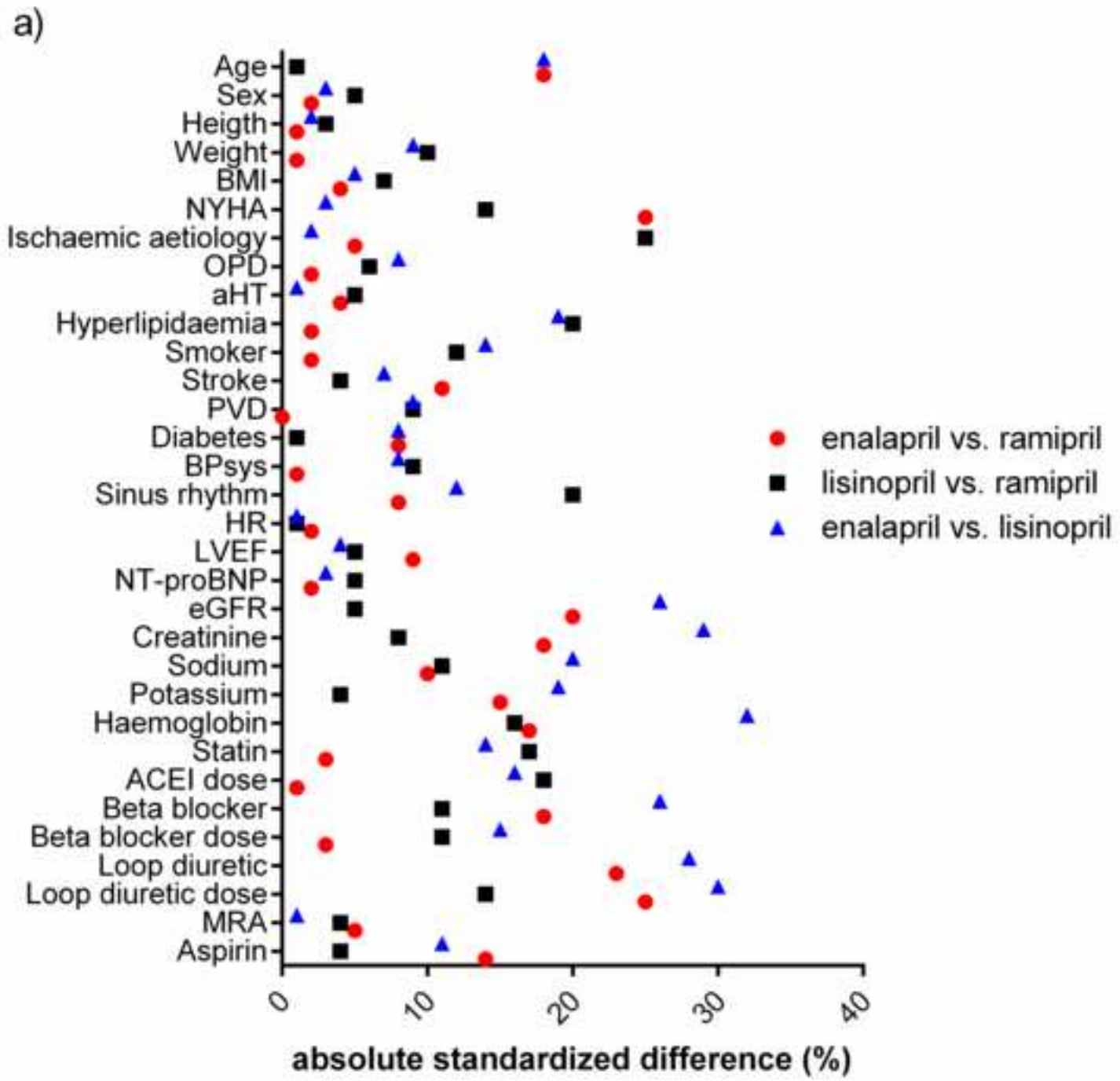

Figure 3 b)

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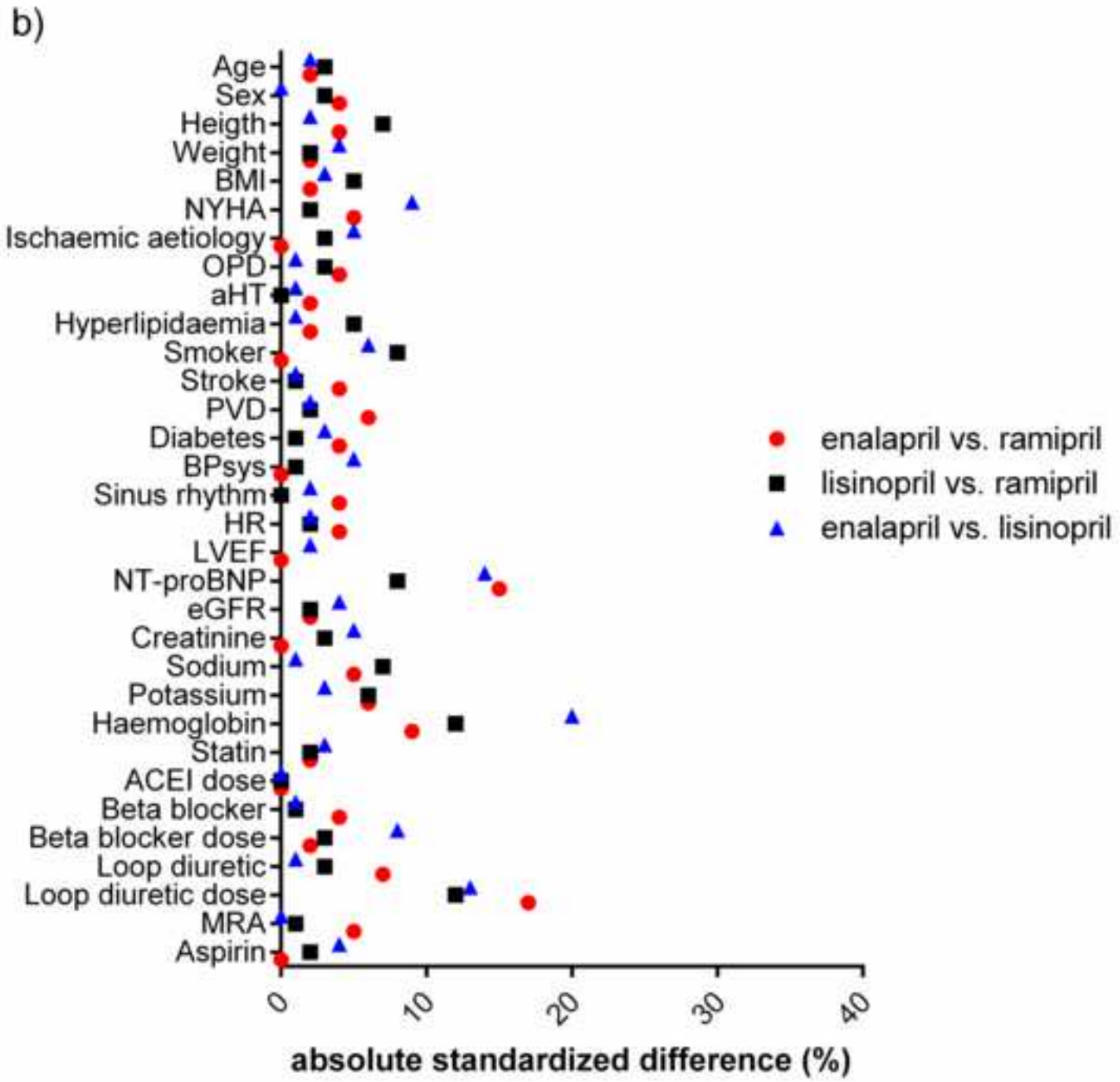

Figure 4

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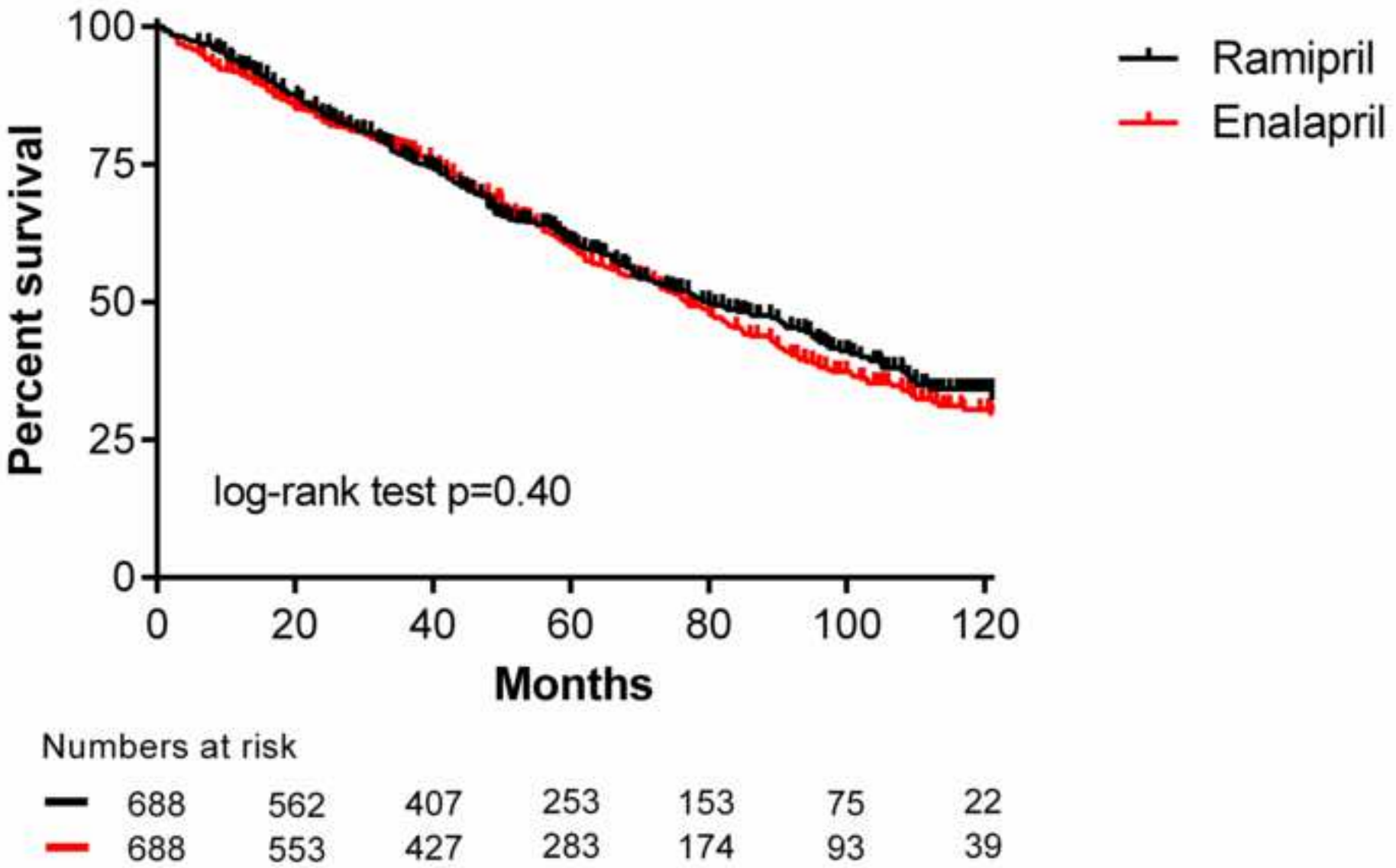

Figure 5

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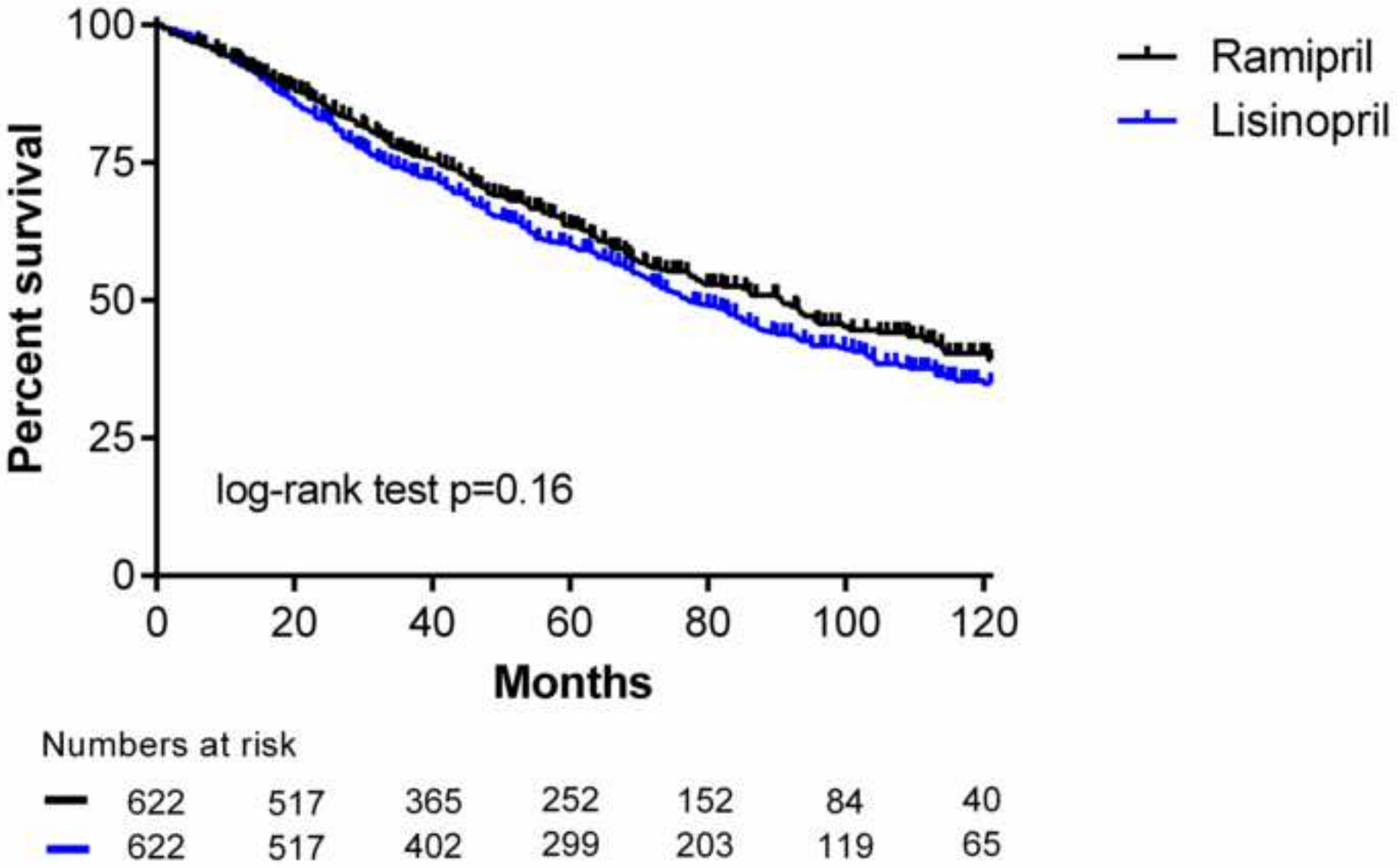

Figure 6

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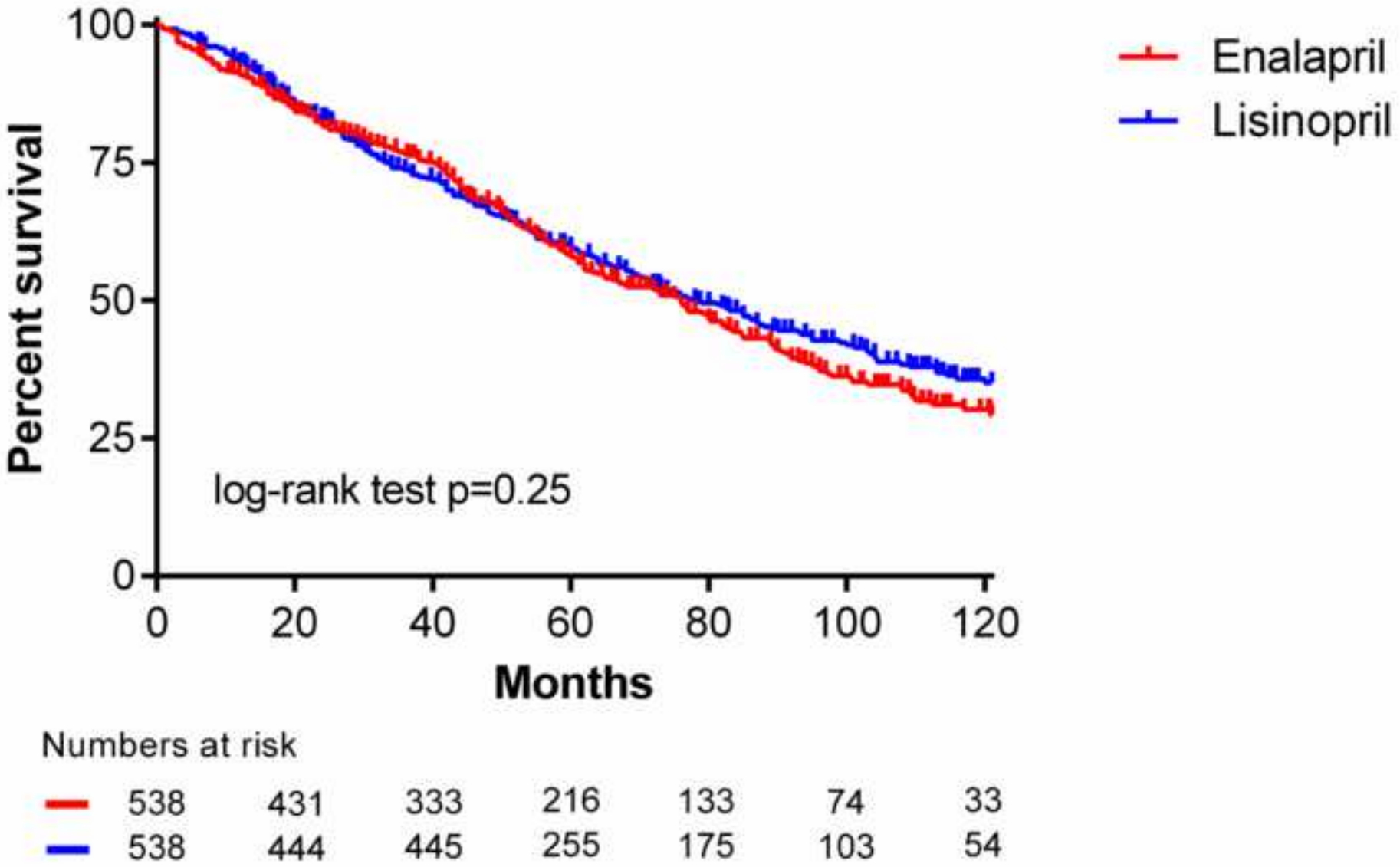

Figure 7

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